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Editorial Comment

Cell adhesion molecules and inflammatory renal diseases

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Cell adhesion molecules (CAMs) are a group of cell surface molecules capable of binding leukocytes through specific counter-receptors. CAMs are members of the large immunoglobulin superfamily by virtue of their extracellular immunoglobulin-like domains, and are expressed in the kidney in endothelial cells, mesangial cells, and renal tubular epithelial cells (TEC) [1]. Table 1 summarizes the characteristics of two major renal CAMs, ICAM-1 and VCAM-1. Intercellular adhesion molecule-1 (ICAM-1) is a monomeric unpaired cell-surface glycoprotein of 76–114 kDa, and is found in many different cell types in various tissues. Vascular cell adhesion molecule-1 (VCAM-1) is an inducible monomeric cell-surface glycoprotein of 110 kDa which is not only expressed on vascular endothelium as its name implies, but also on extravascular sites such as mesangial cells and TEC.

ICAM-1 and VCAM-1 are induced in the kidney in immunologically mediated renal diseases. This induction is caused by interferons and certain cytokines, namely TNF-α and IL-1. Cytomegalovirus is also able to enhance directly ICAM-1 expression on cultured proximal TEC [2], and perhaps also *in vivo*.

The expression of ICAM-1 is enhanced in various inflammatory renal disease states, and it has been speculated that upregulation of CAMs confers increased 'stickiness' to the kidney, thereby promoting leukocyte-mediated renal injury [3]. In human renal allograft rejection, ICAM-1 expression is prominent on renal TEC [4,5], paralleling MHC class II expression [6]. Increased glomerular ICAM-1 expression can be demonstrated in rapidly progressive glomerulonephritis, lupus nephritis and some other glomerulonephritides [7]. The enhanced glomerular ICAM-1 expression in these diseases is sometimes accompanied by increased tubular ICAM-1 staining at the luminal side. The increased tubular ICAM-1 expression correlates with the presence of LFA-1 positive intratubular leukocytes [7]. VCAM-1 expression is also enhanced in inflammatory renal diseases, including crescentic nephritis, vasculitis, interstitial nephritis, and allograft rejection [8,9]. Up-regulation of VCAM-1 is particularly striking in proximal TEC and endothelial cells.

Table 1. Characteristics of the cell adhesion molecules ICAM-1 and VCAM-1

Molecule	ICAM-1	VCAM-1
Ig-like domains	5	7, 6 or 3
Conter-receptor	LFA-1	VLA-4
	Mac-1	$\alpha_4\beta_7$
	CD43	
Inducing cytokines	TNF-α, IL-1	TNF-α, IL-1
	IFN-γ	IFN-γ
Chromosomal location	19	1

In our own studies we investigated ICAM-1 and VCAM-1 expression in murine models of autoimmune renal injury and found that CAMs are up-regulated in the kidney of MRL/*lpr* and (NZBxNZW)F_1 mice with lupus nephritis [3,10]. Low constitutive expression is found in normal mice in glomeruli and proximal tubules. Up-regulation in autoimmune strains is particularly prominent in proximal tubules, endothelium and mesangial cells. TNF-α and IL-1 are present at high levels in the kidneys of autoimmune MRL/*lpr* and (NZBxNZW)F_1 mice [11,12], and could be directly responsible for the increased expression of ICAM-1 and VCAM-1 in the kidney of these autoimmune strains.

In vitro we have demonstrated that ICAM-1 and VCAM-1 are rapidly induced in cultured TEC in response to TNF-α, IL-1 and IFN-γ [10,13]. Peak expression occurs within 6 h, and involves translation of mRNA and *de-novo* transcription. It also appears that a down-regulation-resistant type of protein kinase C is involved in the induction in response to the cytokines TNF-α and IL-1 [14,15]. Commonly used immunosuppressants such as cyclosporin A, steroids and azathioprine are unable to block the cytokine-induced expression of ICAM-1 and VCAM-1 *in vitro*; this does not exclude an inhibitory effect *in vivo* through reduced expression of cytokines [16].

Cytokine-stimulated monolayers of TEC become more adhesive for leukocytes (T cells, monocytic cells). This adherence can be blocked with monoclonal antibodies (MAb) targeting ICAM-1 and VCAM-1, and also by blocking the counter-receptors LFA-1 and VLA-4 respectively. Antigen presentation by TEC can also be inhibited with anti-ICAM-1 and anti-LFA-1 monoclonal antibody treatment *in vitro* [13]. Others have shown that the cytotoxic action of T cells for

TEC can be inhibited with anti-ICAM-1/anti-LFA-1 MAb [17]. Thus, TEC expression of adhesion molecules such as ICAM-1 confers enhanced stickiness and immune reactivity for T cells, and may therefore promote immune renal injury.

What is the *in-vivo* significance of these inducible CAMs in renal injury? Certain CAMs have a well-known structural (architectural) function in the kidney in that they play an essential role in cell–cell contact. Thus, NCAM (neural cell adhesion molecule) is a Ca^{2+}-independent cell–cell adhesion molecule member of the immunoglobulin superfamily that causes renal tubular cell binding through homophilic interaction among NCAM molecules [18]. Cadherins such as uvomorulin (E-cadherin) and N-cadherin are Ca^{2+}-dependent CAMs with structural function and cell-polarity-inducing characteristics in the kidney [19]. Both NCAM and the cadherins also play an important role in morphogenesis and nephron development. CD31 (also termed PECAM-1), a 6 Ig extracellular domain member of the immunoglobulin superfamily, is another example of a CAM that is capable of homophilic (and possibly heterophilic) cell–cell interaction in the kidney [20], thus playing a role in kidney structure.

ICAM-1 and VCAM-1, however, do not appear to have primarily a structural function. We have shown that kidney cryostat section from MRL/*lpr* mice display a significant increase in the adherence for T cells and monocytes when compared with sections obtained from normal mice [3]. This adherence can be blocked to various degrees with antibodies targeting ICAM-1 or VCAM-1. These experiments directly demonstrate that the kidney parenchyma becomes more sticky for inflammatory cells in murine autoimmune renal disease, and that this enhanced stickiness is caused predominantly by ICAM-1 and VCAM-1.

Several MAb against different adhesion molecules have been tested for therapeutic intervention in experimental models of renal inflammation. Anti-ICAM-1 and anti-LFA-1 MAb have already been tried in human kidney allograft rejection.

A murine anti-human ICAM-1 MAb (R6.5) has been used both prophylactically and therapeutically in Cynomolgus monkeys receiving kidney allografts [21]. While this monoclonal antibody clearly prolongs cardiac and renal allograft survival in Cynomolgus monkeys, its clinical usefulness needs to be confirmed. A small human trial using the same ICAM-1 antibody (BIRR1, previously termed R6.5) showed limited usefulness in controlling allograft rejection and possibly reperfusion injury [22]. An anti-LFA-1 antibody used in a small clinical trial to treat acute renal transplant rejection showed no effectiveness [23].

A recent study using mouse heart allografts nicely demonstrated that tolerance could be induced against major histocompatibility barriers when anti-ICAM-1 and anti-LFA-1 monoclonal antibodies were used together [24]. Although the mechanisms of tolerance induction in this animal model remain to be determined, this promising study may have important consequences for prevention and treatment of human renal allograft rejection.

In a recent study of hereditary autoimmune tubulointerstitial nephritis in the mouse (kdkd mouse of the CBA/Ca strain) it was shown that ICAM-1 is overexpressed in the kidney of these mice with interstitial nephritis [25]. Treatment with an anti-ICAM-1 MAb reduced the leukocyte infiltration, and also reduced proteinuria. In rat models of nephrotoxic serum nephritis and crescentic glomerulonephritis it could be shown that treatment with anti-ICAM-1 or anti-LFA-1 MAb reduced proteinuria and glomerular inflammation [26–28].

In summary, the cell adhesion molecules ICAM-1 and VCAM-1 play an important role in immune-mediated renal diseases. By conferring increased adhesiveness to the renal parenchyma they promote the adhesion of inflammatory leukocytes. Targeting these adhesion molecules with MAb may show promising effects in various renal diseases and in allograft rejection.

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